REMARKS

I. Amendments to the Claims

After entry of this amendment, claims 31-62 and 81-108 will be all the claims pending in the application.

Of these claims, claims 31-62 are withdrawn from consideration.

Claims 71-80 have been canceled.

Claims 81-108 have been amended to recite "isolated" polypeptides.

Claims reciting sequence alignment (claims 81, 82, 84-86, 89, 92-96, 99, 102, and 104-106) have been amended to recite "the amino acid at the position corresponding by sequence alignment *with SEQ ID NO:1* to position 118 of SEQ ID NO:1." Support for reciting SEQ ID NO:1 as a reference sequence can be found in the present specification, for example at page 50 (indicating that the position corresponding to Ser 118 of SEQ ID NO: 1 can be identified by the alignment of the sequence of a mutant BAD or fragment of a mutant BAD with SEQ ID NO: 1).

II. Claim Rejections Under 35 U.S.C. § 101

At page 2 of the Office Action, claims 71-108 were rejected under 35 U.S.C. § 101 as being directed to non-statutory subject matter.

Specifically, the Examiner indicated that the claims do not recite isolated or purified compounds, and therefore recite non-patentable products of nature.

Claims 71-80 have been canceled, rendering the rejection moot as to these claims. With regard to the remaining claims, Applicants have amended the claims to recite "isolated" polypeptides, as suggested by the Examiner.

Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

III. Claim Rejections Under 35 U.S.C. § 112, First Paragraph - Written Description

A. Amino Acids Conservative for Alanine

At page 3, paragraph 1 of the Office Action, claims 71-76, 78-83, 85-93, 95-103, and 105-108 were rejected under 35 U.S.C. § 112, first paragraph, for lack of written description.

Specifically, the Examiner asserted that the limitation of "an amino acid conservative for alanine" has no clear support in the specification or the claims as originally filed. According to the Examiner, although the specification discloses support for replacement of serine at amino acid position 118 of SEQ ID NO:1 with alanine or amino acids other than serine, there is no mention of amino acids conservative for alanine at the amino acid position 118 of SEQ ID NO:1.

Applicants respectfully traverse this aspect of the written description rejection, for at least the following reasons.

First, Applicants note that in previous Office Actions, the Examiner did not find an absence of support for this term. In fact, at page 3, paragraph 2 of the Office Action dated

February 10, 2005, the Examiner stated that a claim reciting this language (claim 3, reciting that "the amino acid at position 118 of SEQ ID NO:1 is alanine *or an amino acid conservative for alanine*") was directed to allowable subject matter, and would be allowable if rewritten in independent form.

Furthermore, Applicants submit that support for recitation of an amino acid conservative for alanine would be understood to be inherent by the skilled artisan.

First, it is well known in the art that amino acids can be grouped as follows:

(1) amino acids with aliphatic side chains: glycine, alanine, valine, leucine, isoleucine, methionine, and proline;

(2) amino acids with aromatic side chains: phenylalanine, tyrosine, and tryptophan;

(3) amino acids with hydroxyl-containing aliphatic side chains: serine and threonine;

(4) sulfhydryl-containing amino acids: cysteine;

(5) amino acids with basic side chains: lysine, arginine, and histidine;

(6) amino acids with acidic side chains: aspartic acid and glutamic acid; and

(7) amino acids with carboxamide-containing side chains: asparagine and glutamine. (See, e.g., Lubert Stryer et al., Biochemistry, 5th edition, W.H. Freeman and Co., New York (2002), available online at http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=stryer.section.365).

Second, the specification teaches that the effect of substitution of the amino acid at position 118 of SEQ ID NO:1 differs depending on the substituted amino acid. In particular, the present inventors have shown that substitution of serine at this position with alanine promotes cell death activity. In addition, substitution at this position with an amino acid that is not alanine or an amino acid conservative for alanine (aspartic acid, containing an acidic side chain) results in loss of pro-apoptotic activity (see, e.g., Fig. 12(c) of the present specification). Thus, a person of ordinary skill in the art would have recognized that amino acids conservative for alanine would have the same apoptosis-promoting function as alanine when placed at position 118, and would have known that amino acids conservative for alanine could be selected from glycine, valine, leucine, isoleucine, methionine, and proline, because each of these amino acids has an aliphatic side chain.

Accordingly, Applicants respectfully request reconsideration and withdrawal of this aspect of the written description rejection.

B. Amino Acids 106-132

At page 3, paragraph 2 of the Office Action, claims 99-108 were rejected under 35 U.S.C. § 112, first paragraph, for lack of written description.

Specifically, the Examiner asserted that the specific sequence of amino acids 106-132 of SEQ ID NO:1, as recited in claims 99 and 103-108, has no clear support in the specification and the claims as originally filed. The Examiner stated that the specification instead supports amino

acids 106-131 of SEQ ID NO:1, corresponding to amino acids 143-168 of SEQ ID NO:2 (citing page 43, lines 5-8, and Table 1 at page 41).

The Examiner also asserted that the specific sequence of amino acids 78-132 of SEQ ID NO:1 as recited in claims 100-102 is not supported in the specification and the claims as originally filed.

With regard to claims 93 and 101-108, Applicants submit that amino acids 106-132 of SEQ ID NO:1 (27 amino acids) correspond to amino acids 143-168 of SEQ ID NO:2 (26 amino acids), because SEQ ID NO:1 has a lysine residue, at position 127, that is missing from SEQ ID NO:2 (see Table I). It is this gap that results in the one amino acid difference in the length of the BH3 domains. Thus, the BH3 domain recited in claims 93 and 101-108 is supported in the specification.

With regard to claims 100-102, Applicants note that these claims were intended to recite "amino acids *106*-132" rather than "*78*-132." This typographical error has been corrected in the present amendments to the claims.

Applicants respectfully request reconsideration and withdrawal of this aspect of the written description rejection.

C. Variant BAD Polypeptides

At pages 5-19 of the Office Action, claims 71-108 were rejected under 35 U.S.C. § 112, first paragraph, for lack of written description.

1) Position corresponding by sequence alignment: Beginning at page 9, paragraph A of the Office Action, the Examiner asserted that because there is no reference point for sequence alignment, it is not clear which amino acid is referred to by the term "amino acid at the position corresponding by sequence alignment to position 118 of SEQ ID NO:1." Thus, according to the Examiner, the claims encompass variants of SEQ ID NO:1 that could have substitution with alanine at any position throughout the length of the full-length polypeptide (with regard to claims 71-80) or the recited fragments (with regard to the remaining claims). The Examiner concluded that in view of the unpredictability in the art of protein engineering, the claimed variants would not be expected to possess the recited function.

In response, Applicants note that a "reference point" is not needed in order to align two sequences. The entire sequence, rather than a single amino acid, is used to align one sequence with another.

The Examiner may possibly be referring to the fact that the claims do not explicitly recite that the sequence with which the claimed polypeptides are to be aligned is SEQ ID NO:1. In order to clarify the claimed invention, Applicants have amended the claims to recite "the position corresponding by sequence alignment *with SEQ ID NO:1* to position 118 of SEQ ID NO:1."

Applicants respectfully submit that "the amino acid position corresponding by sequence alignment with SEQ ID NO:1 to position 118 of SEQ ID NO: 1" is clearly defined in the specification with regard to any of the homologues and fragments encompassed by the present claims.

For example, pages 9, 41 and 45 of the specification describe how sequence alignment allows identification of regions of sequence homology (see also page 25 and 26 of the Amendment filed November 12, 2004 in the present application). In particular, the specification notes that sequence alignment allows "identification of the serine, or other amino acid, at a position corresponding to the serine at position 118 of SEQ ID NO: 1" (page 45, lines 8-11). Similarly, page 50 of the specification indicates that the position corresponding to Ser 118 of SEQ ID NO: 1 can be identified by the alignment of the sequence of a mutant BAD or fragment of a mutant BAD with SEQ ID NO: 1. In addition, Table 1 at page 41 illustrates how sequence alignment can be used to identify the position corresponding to 118 of SEQ ID NO: 1 in the mouse BAD sequences, which vary slightly from SEQ ID NO: 1.

In addition, what is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. *Hybritech Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1369, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). In this regard, Applicants submit that sequence alignment is well known in the art. For example, numerous widely available references describe the use of sequence alignment to compare related polypeptide sequences (see, e.g., Tatusova and Madden (1999), "Blast 2 sequences - a new tool for comparing protein and nucleotide sequences," FEMS Microbiol. Lett. 174:247-250; Altschul et al. (1997), "Gapped BLAST and PSI-BLAST: a new generation of protein database search programs," Nucleic Acids Res. 25:3389-3402 (submitted with the July 7, 2005 Amendment); and the BCM Search Launcher: Multiple Sequence Alignments).

Finally, Applicants note that the Examiner has used sequence alignment himself, in the §102(e) rejection set forth at page 28 of the present Office Action (see below), to determine that U.S. Patent No. 5,955,703 describes an amino acid sequence that is 75% similar to SEQ ID NO:1 and has a threonine at the position corresponding to position 118 of SEQ ID NO:1. It is not clear to Applicants how the Examiner can use sequence alignment to determine the position of the threonine, yet at the same time maintain that a person of ordinary skill in the art would not know which amino acid is referred to by the term "amino acid at the position corresponding by sequence alignment to position 118 of SEQ ID NO:1."

Because a person of ordinary skill in the art would have known how to perform the recited sequence alignment given the information described in the specification and the art, Applicants respectfully request reconsideration and withdrawal of this aspect of the written description rejection.

2) **Variants of full-length SEQ ID NO:1:** Beginning at page 11, paragraph B of the Office Action, the Examiner asserted that claims 71-74 and 76-80 encompass a variant BAD sequence that does not necessarily have the whole BH3 domain (defined by the Examiner as amino acids 114-122 of SEQ ID NO:1).

The Examiner noted that the BH3 domain is necessary for the binding of BAD to Bcl-X_L or Bcl-2, and that the binding step is necessary for inducing apoptosis. Therefore, the Examiner concluded that one could not predict that the claimed variant polypeptides would possess the recited function.

Claims 71-80 have been canceled, rendering this aspect of the written description rejection moot.

3) **Variants of fragments comprising the BH3 domain:** Beginning at page 12, paragraph C of the Office Action, the Examiner indicated that the specification does not support polypeptides comprising a BH3 domain that has any mutation other than substitution of the serine with an alanine at position 118.

First, the Examiner asserted that a person of ordinary skill in the art would not have known which amino acids in the BH3 domain, other than serine 118, could be altered by substitution, deletion, or addition. Second, the Examiner asserted that a person of ordinary skill in the art would not have known which amino acids, other than alanine or glycine, could be substituted for the serine at position 118 to yield a functional polypeptide.

With regard to the Examiner's first assertion, Applicants submit that a person of ordinary skill in the art would have known which amino acids in the BH3 domain were reasonably likely to be essential for function. As noted in the November 12 Amendment, the BH3 domain of BAD and other related proteins was so well-characterized at the time of invention that a person of ordinary skill in the art would have been able to predict with reasonable certainty the effect that specific mutations within the BH3 domain would have on the function of this peptide.

In particular, sequence alignments between various BAD polypeptides and between BAD and related proteins can be used to determine which residues are conserved and therefore likely to be essential for function. For example, Table I at page 41 of the present specification shows

the human BAD of SEQ ID NO:1 aligned against the murine BAD of SEQ ID NOs: 2 and 3. In Table I, the amino acids common between all three of the BAD amino acid sequences are denoted in bold type.

In addition, several journal articles demonstrate the use of sequence alignments to indicate primary sequence homology between the critical BH3 domains of BAD and other apoptosis regulators of the BCL-2 family. See, e.g., Zha et al., *BH3 Domain of BAD is Required fro Heterodimerization with BC-X_L and Pro-apoptotic Activity*, JBC 272:24101 (1997) (Fig. 3A) and Kelekar et al., *Bad is a BH3 Domain-Containing Protein that Forms an Inactivating Dimer with Bcl-X_L*, Mol. Cell. Biol. 17:7040 (1997) (Fig. 3).

Furthermore, functional mutants of BAD can be designed by analogy to other well-studied members of the BCL-2 family. The crystal structure of BAK, for example, had been solved as of the filing date of the present application. Sattler et al., *Structure of the Bcl-X_L-Bak Complex: Recognition Between Regulators of Apoptosis*, Science 275:983 (1997) provides considerable information regarding the relationship between the structure and the function of BAK, particularly the relationship between the structure of the BH3 domain of BAK and the function of that domain. In particular, the authors test the binding affinities of numerous mutant BAK BH3-containing peptides, and demonstrate that the BAK peptide adopts an amphipathic α-helix that interacts with Bcl-X_L through hydrophobic and electrostatic interactions.

In addition, the relationship between the structure and the function of the BAD protein itself has also been investigated. Fig. 2B of Zha et al., for example, shows the predicted structure of the BH3 amphipathic α-helix of BAD, providing views of the hydrophobic and polar surfaces

and indicating the likely positions of the amino acid residues. Zha et al. also use site-directed mutagenesis to substitute individual amino acids within the BH3 region of BAD, and assess the effect of the various mutations on both *in vitro* and *in vivo* heterodimerization with Bcl-X_L, and on cell death promoting activity (Figs. 5 and 6). Thus, one of ordinary skill in the art would have been able to predict with reasonable certainty the effect that specific mutations would have on the function of BAD.

With regard to the Examiner's second assertion, Applicants assert that a person of ordinary skill in the art would have known which amino acids are "conservative for alanine," and thus would have known which amino acids could be substituted for the serine at position 118 to yield a functional polypeptide (see above).

Accordingly, Applicants respectfully request reconsideration and withdrawal of this aspect of the written description rejection.

4) **Binding to Bcl-X_L or Bcl-2:** At page 15, paragraph E of the Office Action, the Examiner stated that binding to Bcl-X_L or Bcl-2 is not a definitive function that defines the claimed BAD polypeptide, and does not correlate with the structure of a BH3 domain, because there are other polypeptides with completely different structure that bind to Bcl-X_L or Bcl-2, via a different domain, such as BAX which binds to Bcl-2 via its BH1 or BH2 domain (citing Yin et al, 1994 Nature, 369: 321-323).

The claims have been amended by deleting recitation of Bcl-X_L or Bcl-2 binding, rendering this aspect of the written description rejection moot.

IV. Rejection Under 35 U.S.C. § 112, Second Paragraph - Indefiniteness

At page 4 of the Office Action, claims 71-108 were rejected as indefinite.

Specifically, the Examiner asserted that the language "position corresponding by sequence alignment to position 118 of SEQ 1D NO:1" renders the claims indefinite, because one cannot determine which amino acid is the reference point for sequence alignment.

Applicants note that this issue is discussed above, in the section relating to the written description rejection. Applicants submit that the phrase "position corresponding by sequence alignment with SEQ ID NO:1 to position 118 of SEQ 1D NO:1" particularly points out and distinctly claims the subject matter which Applicants regard as the invention.

Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

V. Rejections Under 35 U.S.C. § 112, First Paragraph, Enablement

At page 19 of the Office Action, claims 71-108 were rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement.

Specifically, the Examiner asserted that the specification, while enabling a polypeptide comprising SEQ ID NO: 1 wherein the amino acid at position 118 is alanine, does not enable any of the variants recited in the present claims.

Similar to the written description rejection (discussed above), the Examiner stated that the claims encompass variants of SEQ ID NO:1 wherein the variant could have substitution with alanine at any amino acid throughout the whole length of SEQ ID NO:1, or at any position in the recited fragments. The Examiner also stated that the claims encompass variants of SEQ ID NO:1 wherein the entire BH3 domain is lacking, or wherein any of the amino acids in the BH3 domain could have any deletion, addition, or substitution. Further, the Examiner stated that the amino acid at position 118 could be any amino acids, other than alanine or glycine.

The Examiner concluded that one cannot predict whether the claimed polypeptides will have the recited function, in view of the fact that it is well known in the art that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristics of a protein, and that protein chemistry is probably one of the most unpredictable areas of biotechnology. In this regard, the Examiner stated that it is known in the art that a mutated BH3 domain, such as the BH3 domain of BID, with two substitutions at L90A and D95A, loses the ability to cause cytochrome c release, and thus subsequent apoptosis (citing Letai, et al, p.184, second column, last four lines of the first paragraph under Results).

Claims 71-80 have been canceled, rendering this rejection moot as to those claims.

With regard to the remaining claims, Applicants respectfully submit that because the structure and function of the BH3 domains of BAD and other related proteins had been extensively analyzed (see above for more detail), a person of ordinary skill in the art would have

known how to design mutant polypeptides that would be reasonably certain to retain the recited activity. In addition, because an assay for determining cell death promoting activity *in vitro* is described at pages 99-100, the specification enables the identification of variants within the scope of the claims.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the enablement rejection.

VI. Rejections Under 35 U.S.C. § 102 - Anticipation

A. Claims 71-108

At page 25 of the Office Action, claims 71-108 were rejected under 35 U.S.C. § 102(e) as being anticipated by US Patent No. 5,965,703, for reasons already of record in the Office Action dated February 10, 2005.

Specifically, the Examiner asserted that the specification only describes the results of the alignment, i.e. that the position corresponding to position 118 of SEQ ID NO:1 is determined by alignment of mutant BAD with SEQ ID NO:1 (p.9), that the alignment "allows" identification of regions of sequence homology, such as the BH3 domain, or the serine at position of 118 of SEQ ID NO:1 (p.45), and the actual alignment of different sequences in table 1 on page 41. Thus the Examiner concluded that the term "the amino acid at the position corresponding by sequence alignment to position 118 of SEQ .1 D NO: 1" is not defined by the specification, nor is it limiting, and that because one cannot determine which amino acid is the reference point for

sequence alignment in the claims, any amino acid could correspond by sequence alignment to position 118 of SEQ ID NO:1.

Claims 71-80 have been canceled, rendering the rejection moot as to these claims.

With regard to the remaining claims, Applicants note that the position defined in the present claims as "the position corresponding by sequence alignment with SEQ ID NO:1 to position 118 of SEQ 1D NO: 1" is clearly defined by the specification. Further, a person of ordinary skill in the art would know that serine is not "alanine or an amino acid conservative for alanine." SEQ ID NO: 2 of the '703 patent includes a serine residue at position 118. Accordingly, SEQ ID NO: 2 does not anticipate the presently claimed polypeptides.

Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

B. Claims 78 and 79

At page 28 of the Office Action, claims 78 and 79 were rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,965,703.

Specifically, the Examiner stated that the '703 patent teaches a mouse BAD sequence that is 75% similar to SEQ ID NO:1 of the present application, wherein the amino acid at the position corresponding by sequence alignment to position 118 of SEQ ID NO:1 is threonine.

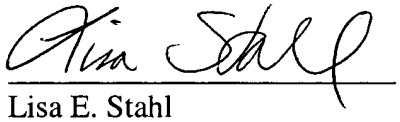
Claims 78 and 79 have been canceled. Thus, this rejection is moot.

VII. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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